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Unlucky versus coincidence: Dual hepato-pancreatico biliary diagnoses in a six-year-old

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ABSTRACT

We describe a case of inflammatory myofibroblastic tumor presenting as a head of pancreas mass in a six-year-old girl. The etiology of such lesions is elusive, with a poorly understood malignant potential. One hypothesis is that they occur in areas of inflammation and trauma. The tumor occurred two years after this same patient had a Type I choledochal cyst excised with Roux-En-Y hepaticojejunostomy.

Inflammatory myofibroblastic tumors (IMTs) have undergone many nomenclature changes in recent years, reflecting incomplete understanding of their etiology, pathogenesis and clinical behavior [1]. Also known as inflammatory pseudotumors or plasma cell granulomas, they are rare neoplasms [1], and rarer still in children. This report presents a child who developed an IMT in a post-operative field.

1. Case report

A 6-year-old female presented with a one-month history of fatigue, vomiting, anorexia, early satiety and weight loss. She had no abdominal pain and physical examination was unremarkable with neither jaundice nor a palpable abdominal mass being noted.

Ultrasound investigation revealed a right hypochondrial mass. A portal venous contrast computed tomography (CT) study of the abdomen showed a 6 × 6.2 cm mass arising from the head of pancreas, with atrophy of the pancreatic body and tail. No biliary or pancreatic ductal dilatation was noted and there were no other lesions (Fig. 1). Blood tests showed a microcytic anemia with normal inflammatory markers, normal hepatic and renal function, a lipase of 79 U/L (normal value < 60 U/L), and a normal ferritin.

Two years previously, a Type I choledochal cyst had been diagnosed in this patient after she presented with obstructive jaundice. She underwent an uncomplicated choledochocystectomy with Roux-En-Y hepaticojejunostomy. Pathological examination of the resected specimen demonstrated a choledochal cyst with chronic inflammation and fibrosis. She made a full recovery, and 6 monthly post-operative ultrasound scans were normal prior to her symptomatic presentation.

An endoscopic retrograde cholangiopancreatogram (ERCP) was organized to obtain a tissue diagnosis. Examination of the biopsy specimens taken showed a stromal lesion of intermediate biological behavior, favoring an IMT. The biopsies were positive for anaplastic lymphoma kinase (ALK), B-cell lymphoma 2 (BCL2) and Cyclin D1; human herpesvirus 8 (HHV8) was negative.

Following multidisciplinary consultation, crizotinib (Pfizer, New York City, USA), an ALK and ROS1 inhibitor, was prescribed prior to planned resection. Shrinkage of the tumor to 2.8 × 2.4 cm over 4 months was observed. The patient went on to have a pancreaticoduodenectomy (Fig. 2) with posterior pancreaticogastrostomy and anterior gastrojejunostomy (Fig. 3). The previous hepaticojejunostomy was left undisturbed. Histological margins were tumor free. She made a speedy recovery but was readmitted a short time later with delayed gastric emptying which resolved with parental nutrition support and gut rest. She remains well nine months later, with no evidence of recurrence.

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Fig. 1. Coronal and axial computed tomography images demonstrating the head of pancreas mass measuring approximately 6 × 6 cm.

2. Discussion

IMTs are rare, solid lesions occurring most commonly in the bronchial tree, retroperitoneum and abdominal cavity [2]. When examined histologically, they are composed of fibroblast and myofibroblast infiltrates with a background chronic inflammatory infiltrate of eosinophils, plasma cells and lymphocytes. Although they clinically and radiologically mimic neoplasms, IMTs have questionable potential for aggressive behavior. Recognition of ALK gene rearrangement and cytogenetic aberrations support the concept of IMTs being a neoplastic lesion and as such the World Health Organisation classifies them as a distinctive neoplasm with intermediate biological behavior [2]. Complete surgical excision appears to be curative although cases of metastatic disease have been reported [3]. Evidence suggests that pathological features of atypia, p53 expression and aneuploidy may predict IMTs with more aggressive potential [4].

Several biological markers have been identified as having diagnostic and therapeutic importance, although these are not specific for IMTs. Anaplastic lymphoma kinase (ALK) rearrangements on chromosome 2p23 result in aberrant ALK expression in 40–50% of IMTs [5,6]. Children and young adults diagnosed with IMTs appear more likely than adults over the age of 40 to harbor ALK rearrangements in the myofibroblastic component of the tumor; the inflammatory component does not exhibit this change. ALK inhibitors such as crizotinib are therefore potentially of benefit.

Fig. 2. Pancreaticoduodenectomy specimen. Arrow points to area of IMT which had a rubbery consistency.

Given the location of our patient's disease and the desire to perform a less extensive, albeit complete, resection, neo-adjuvant treatment was used with the intention of shrinking the lesion. IMT response to crizotinib has been described. Butrynski et al. [6] reported a partial response to crizotinib in a 44-year-old man with diffuse intraabdominal IMT harboring ALK rearrangement detected by fluorescent in situ hybridisation (FISH). Following surgical debulking, the initial substantial response to therapy lasted 6 months, after which the tumor began to re-grow. After further surgical debulking of the recurrent tumor, the patient remains on long-term crizotinib with no radiological evidence of recurrence. The second patient in Butrynski's report was a 21-year-old male with a gastric IMT. The resected specimen was negative for ALT rearrangement and when recurrent disease was detected five months later, crizotinib was initiated and re-staging showed worsening of disease with no response to therapy. The authors concluded that there was potential for long-term response in favorable tumor cell populations to crizotinib; this formed the rationale for administration of the drug to the patient described in our paper. Her response gives further support to Butrynski's findings. Further, targeted ALK therapy in pediatric malignancies was found to be safe in a Phase 1 trial in patients aged 12 months to 22 years [7]. Anti-tumor activity was enriched in patients with known ALK rearrangements and the drug was well tolerated. Phase 2 of this US trial is due for completion in 2017 [8].

The etiology of IMTs has remained elusive since they were first described in 1939 [9]. Neoplastic, infectious, autoimmune and genetic etiologies have all been proposed. Identification of human herpesvirus 8 (HHV-8) and Epstein–Barr virus (EBV) DNA sequences in IMT specimens was initially promising [10,11] although this has not been substantiated in pediatric case series [3,12]. Human interleukin 6 (IL-6) and cyclin D1 overexpression have been reported in a case series of 7 patients [13], and p53 modulated alterations have been implicated in those IMTs harboring malignant transformation [2].

Accurate demographic data regarding anatomical sites affected by IMTs are difficult to obtain given the interchangeable terms historically used to describe these lesions. Janik et al. [14] collated 274 pediatric cases of IMTs reported in the literature: this is perhaps the largest summative series. One third of IMTs occurred in the pulmonary tree. Intra-abdominal IMTs made up the majority of extrapulmonary locations with the omentum, retroperitoneum and mesentery being the most common. IMTs have a predilection for patients in the first two decades of life, with the youngest published

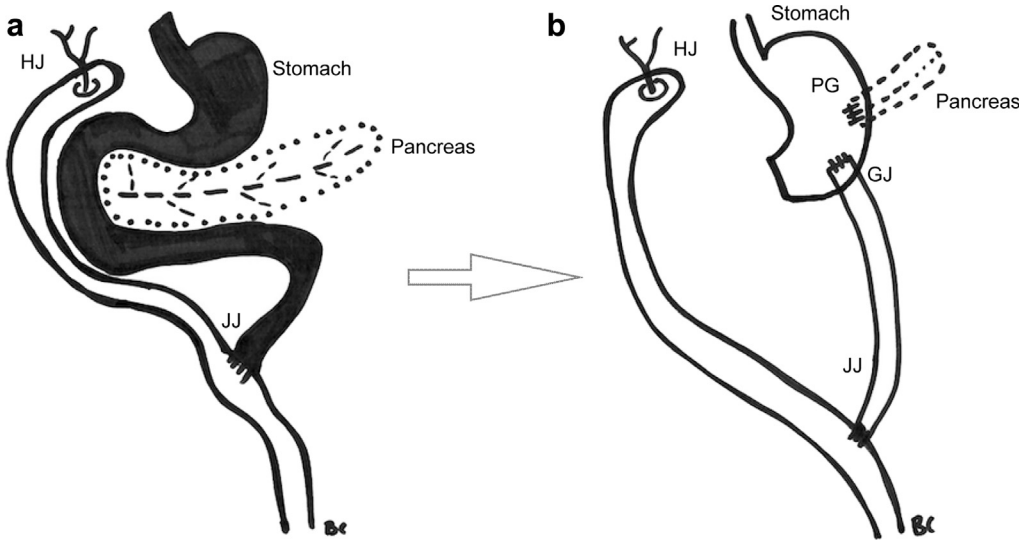

Fig. 3. Representation of a) choledochocystectomy with Roux-En-Y hepatico-jejunostomy. The hepaticojejunostomy was performed in a retrocolic fashion with a 40 cm jejunal limb; and b) pancreatico-duodenectomy with posterior pancreatico-gastrostomy and anterior jeju-jejunostomy. HJ: Hepatico-jejunostomy; JJ: jeju-jejunostomy; GJ: gastro-jejunostomy (anterior stomach); PG: pancreatico-gastrostomy (posterior stomach).

intra-abdominal case being in a 7-day-old infant [15]. Only 28 cases of pediatric pancreatic IMT have been described, with 60% located in the pancreatic head [16].

Controversies abound in discussions about IMTs, particularly regarding their etiology. Some authors consider them a reactive proliferation, while to others they represent a true neoplasm. Brunn believed IMTs to be benign proliferative reactions occurring in the lung in his 1939 paper [9]. It was not until the 1990s that the aggressive potential of IMTs was recognized when Meis and Enzinger [17] published a case series of 38 children and adolescents with follow-up data showing significant rates of local and widespread recurrence; 5 patients died from their disease. At this time the term 'inflammatory fibrosarcoma' was used to label the lesions, reflecting the spindle cell proliferation and prominent inflammatory infiltrate. Advancement of genomic and molecular knowledge over time has enabled researchers to identify specific clonal rearrangements such as those involving chromosome 2q, further supporting the neoplastic nature of these lesions.

A unifying cause has yet to be positively identified. There is an antecedent history of tissue trauma in a percentage of patients with IMTs; this may be surgical, immunological, infective or inflammatory [18]. This lends some support to the hypothesis IMTs are an aberrant response to tissue injury. HHV-8 and EBV were initially explored as candidate etiologies with little success. The finding of IL-6 mRNA and protein production in tumor cells is thought to cause some of the systemic symptoms patients with IMT experience; these symptoms resolve on surgical resection of the lesion. Similar findings are seen with the lymph node hyperplastic disorder Castleman disease, prompting some authors to propose there may similar underlying mechanisms at play [10,19,20].

The question of whether IMTs arise in, or adjacent to, postoperative sites is intriguing. Several case reports document IMTs occurring months to years after the resection of neoplasms. Nine years after the successful treatment of a right-sided Wilms tumor, Vujanic et al. [21] report a child who had an intra-abdominal IMT diagnosed. He presented with progressive dysphagia and abdominal swelling and was diagnosed with an IMT involving the gastroeosophageal junction, stomach and liver. The Wilms tumor had been treated with 4 weeks of preoperative chemotherapy followed by a right radical nephrectomy. Four further patients were reported with IMTs following the successful treatment of childhood malignancies. Two patients had Wilms tumors, one a left hemithoracic Askin tumor, and one nodular sclerosing Hodgkin disease. All IMTs subsequently occurred in the post radiotherapy or surgical field, up to 10 years later. Although by no means conclusive, the authors present these cases as anecdotal evidence of increasing incidence of IMTs after treatment of malignancy. This scenario also presents a diagnostic dilemma in differentiating these lesions from primary relapse [22]. A 12-year-old boy had an IMT resected from a post-auricular site that had had an antecedent trauma fifteen days prior. The area had been pierced with a sharp pen, resulting in ulceration with purulent discharge from the site. This was followed by a progressively enlarging mass, prompting resection. Histological examination of this mass revealed an IMT [23]. All such reports are compelling if one considers IMTs to occur in previous sites of surgical or accidental trauma. This could certainly explain the inflammatory component of the lesions. The case we describe supports this link.

All prior abdominal imaging on our patient was retrospectively re-examined. Despite knowledge of her subsequent course, no lesion was found on review of her radiology. Ultrasound has 50–70% sensitivity for detection of pancreatic lesions in adults; this figure is greater in children given the ability of the sonographic waves to penetrate a greater distance given the smaller size of the child and the relatively fat-free intra-abdominal content [24]. CT with intravenous contrast is somewhat more sensitive, detecting 76–92% of pancreatic lesions [25,26]. It is possible that the lesion was missed but prior views of the region were clear, in particular her scan 5 months before her acute presentation.

The debate regarding the etiology of IMTs continues: Are they truly neoplastic or a reactive pseudotumorous proliferation? The case described here gives further evidence favoring a reactive proliferation in a post-surgical field, albeit an aberrant one with, for example, clonal expansion being present. IMTs are rarely diagnosed: rarer still to have two uncommon diagnoses in the one patient. An as yet undiscovered viral, pathological or inflammatory agent has not been precluded as the initiating event. The rarity of IMT and confusion arising from varied historical descriptions of tumors that are recognizably IMT contribute to ongoing difficulties in defining these lesions. Accumulating further case reports, such as this one, will perhaps lead to future insights into causative mechanisms.

Conflicts of interest

None declared.

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